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The purpose of the research supported by this award is to conduct a Phase II clinical trial (study) of an adenovirus/PSA (Ad/PSA) vaccine for the treatment of prostate cancer. Two protocols have been used in the trial: #1 - *Phase II study of Adenovirus/PSA vaccine in men with recurrent prostate cancer after local therapy*; and #2 - *Phase II study of Adenovirus/PSA vaccine in men with hormone refractory prostate cancer*. In the first protocol men with newly recurrent prostate cancer were randomized to one of two arms of the study. Patients in Arm A received the Ad/PSA vaccine only; three injections spaced 30 days apart. Patients in Arm B received androgen deprivation therapy (ADT) followed at day 14 by the Ad/PSA vaccine, again with three injections. In the second protocol men with hormone refractory prostate cancer were injected with the vaccine only, three injections 30 days apart. The patients were followed for toxicity, the development of anti-PSA immune responses, and evidence of a clinical effect of the vaccination. The latter includes changes in serum PSA and prostatic acid phosphatase (PAP) levels and in the PSA doubling times (PSADT). Patients in protocol #2 also have CT and bone scans to monitor

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**INTRODUCTION**

The purpose of the research supported by this award is to conduct a Phase II clinical trial (Study) of an adenovirus/PSA (Ad/PSA) vaccine for the treatment of prostate cancer. Two protocols are being used in the trial: #1 – *Phase II study of adenovirus/PSA vaccine in men with recurrent prostate cancer after local therapy,* and #2 – *Phase II study of adenovirus/PSA vaccine in men with hormone refractory prostate cancer*. In the first protocol men with recent documentation of recurrent prostate cancer are randomized to one of two arms of the study. Patients in Arm A receive the Ad/PSA vaccine only; three injections spaced 30 days apart. Patients in Arm B will receive androgen deprivation therapy (ADT) followed at day 14 by the first of three Ad/PSA injections. In the second protocol men with hormone refractory prostate cancer are injected with the vaccine only, three injections 30 days apart. The patients are followed for toxicity, the development of anti-PSA immune responses, and evidence of a clinical effect of the vaccination. The latter includes changes in serum PSA and prostatic acid phosphatase (PAP), and the PSA doubling times (PSADT). Patients in protocol #2 also have CT and bone scans to monitor their prostate cancer.

**BODY:**

The first year of the award, from April 1, 2007 through March 31, 2008, was occupied by negotiations and submissions of documents to the DOD's PCRP, including the Human Subjects Research Review Board (HSRRB), the FDA, NIH's Recombinant DNA Review Committee (RAC), the University of Iowa IRB, the Iowa City VA Medical Center IRB, and the Iowa City VA Medical Center Research and Development Committee. During the second and third years we have been recruiting patients, evaluating their eligibility, screening them for adherence to our entry criteria, vaccinating them and following their clinical and immunological responses according to the schedule described in the protocols.

**Recruitment –** Patients were initially recruited into the trial from the Urology Clinic in the University of Iowa Hospitals and Clinics (UIHC) and the Urology Service at the adjacent Iowa City VA Medical Center. Additional recruitment was through (1) Referrals from private practice physicians (urologists, medical oncologists, and radiation oncologists) following the mailing of a letter sent to these physicians in the State of Iowa and bordering regions of Nebraska, Missouri, Illinois, Minnesota, and Wisconsin. A follow-up letter to the same physician mailing list was sent in 2009, a third letter was sent following protocol modifications in 2010, and a fourth letter was sent during the 2010 holiday season. Referrals from academic physicians (urologists, medical oncologists, and radiation oncologists) following a mailing of a letter sent to academic and VA medical centers in the same geographic areas covered by the letters to the private practice physicians. Follow-up letters were sent early in 2010 and again at the holiday season. (2) The trial is listed on www.clinicaltrials.gov website. (3) Presentation of results from the Phase II trial of the Ad/PSA vaccine at the annual meeting of the American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO), the ASCO Genitourinary Malignancies Conference, and the Fall Symposium of the Society for Basic Urologic Research (SBUR), and the North Central Section of the American Urologic Association (AUA). (4) Talks to prostate cancer survivor support groups in at the University of Iowa, Mercy Medical Center in Cedar Rapids, IA, and the Us TOO chapter in Rock Island, IL. (4) Publication in the University of Iowa Hospitals and Clinics' *"Pacemaker"* magazine with a "Q & A" with me about the trial. (5) Publication of the trial in the University of Iowa Hospitals and Clinics' *"UI Consult."* This is a communication that is mailed to all physicians on a very large mailing list. The publication reaches a larger group of physicians than did our list for the letters, particularly family practice and general practice physicians. (6) Publication of the trial in the University of Iowa Hospitals

and Clinics' *"Medicine"* magazine. The PI was interviewed and photo graphed for the article. Other participants in the article are the Co-PI of the award Dr. Richard Williams and one of our trial patients. (7) Publication in the Department of Veterans Affairs " *VA Currents,"* that is sent via the internet and hard copy to VA Medical Centers.

We have consented and screened a total of 64 patients for eligibility into the two protocols in the study. Thirty patients were screened for Protocol #1, 22 from the st ate of Iowa and 8 from outside the state. Of these 30, 21 were deemed eligible based upon our inclusion and exclusion criteria; 13 were randomized to Arm A, vaccine only, and 8 were randomized to Arm B, androgen deprivation therapy (ADT) plus vaccin e. Nine subjects failed screening; 1 patient for seminal vesicle involvement at origin al pathology, 1 with a p ositive CT scan, 1 had an infection at the time of screening, 1 had an ineligible screening bilirubin, 1 with a PSADT of less than 6 months, and 3 had a decreased PSA value and are pending further evaluation. One patient had castrate levels of testosterone when evaluated further. And one patient previously reported as a screen failure became eligible and was treated. This su bject was n ot counted twice, even though consented and screened at different time points.

Thirty four patients were consented for Protocol #2; 21 from Iowa and 13 from outside the state. Of these 34, 16 patients have been treated and 1 is still awaiting screening. Seventeen patients have failed screening; 4 failed for positive bone scans wit h exclusionary PSA va lues, 5 for positive CT scan, 1 for additional carcinoma, 5 for declining PSA, 1 for aggressive progression, and one subject died su ddenly prior to study treatment. And one patient previously reported as a screen failure became eligible a nd was trea ted. This subject was not counted twice, even though consented and screened at different time points.

We also ha ve received inquiries b y telephone or e-mail from 347 patients as a r esult of our registering the trial on t he website www.clinicaltrials.gov and other recruitment efforts. During the last quarter, we rec eived 34 inquiries; 25 of which we re phone screen negative, and 9 of which are pending further evaluation.

**Enrollment -** After all approvals were obtained patients enrolled during the current year are listed in Table 1.

**Table 1**
**Patients Enrolled from April 15, 2010 to April 14, 2011**

| Patient ID | Protocol | Arm | Information |
|---|---|---|---|
| APIIAHN-08 | 1 | A | Received all 3 vaccinations and completed visits to 12 months. |
| APIIAHN-09 | 1 | A | Received all 3 vaccinations and completed visits to 9 months. |
| APIIAHN-10 | 1 | A | Received all 3 vaccinations and completed visits to 6 months. |
| APIIAHN-11 | 1 | A | Received all 3 vaccinations and completed visits to 90 days. |
| APIIAHN-12 | 1 | A | Received all 3 vaccinations and completed visits to 74 days. |
| APIIAHN-13 | 1 | A | Received 2 vaccinations and completed visits to 44 days. |
| APIIAADT-06 | 1 | B | Received all 3 vaccinations and completed visits to 9 months. |
| APIIAADT-07 | 1 | B | Received all 3 vaccinations and completed visits to 9 months. |

| | | | |
|---|---|---|---|
| APIIAADT-08 | 1 | B | Received all 3 vaccinations and completed visits to 74 days. |
| APIIB-12 | 2 | --- | Received all 3 vaccinations and completed visits to 9 months. |
| APIIB-13 | 2 | --- | Received all 3 vaccinations and completed visits to 9 months. |
| APIIB-14 | 2 | --- | Received all 3 vaccinations and completed visits to 9 months. |
| APIIB-15 | 2 | --- | Received all 3 vaccinations and completed visits to 90 days. |
| APIIB-16 | 2 | --- | Received all 3 vaccinations and completed visits to 74 days. |
| APIIB-17 | 2 | --- | Received all 3 vaccinations and completed visits to 60 days. |
| APIIB-18 | 2 | --- | Received all 3 vaccinations and completed visits to 60 days. |
| APIIB-19 | 2 | --- | Received 1 vaccination only. |

**Adverse Events –** During the period of report t here were two serious adverse eve nts, both deemed unrelated to the vaccine. They are detailed below.

Patient in Protocol #1

66 year old male subject who was r andomized to arm A of t his study (hormones plus vaccine) received the first of three study injections on the 08/12/10. Had a history of periodontal disease, ear pain, a bunion, ankle pain, kidn ey stones and prostate cancer. He had no histo ry of cardiac issues and no prior ch est pain history. Medic ations included Zoladex on 07/28/10, Casodex, herpes zoster vaccine given on 08/04/10, trazodone. The study requires a routine overnight stay in the clinical research unit for observation after vaccination. On 8/13 /10 in am u pon routine evaluation by the study team, he reported that he had had three hours of chest pain between 3 am and 7 a m on August 13th. He did not infor m the research unit nursing staff in the inpatient unit about this, but instead revealed this to the study team in the morning prior to his planned discharge assessment. Patient stated "he thou ght it was related to sleeping on a hospital bed, and that it had changed character and lo cation at 6 A M, going fr om his ster num to his abdomen". He was pr omptly evaluated by the research team and had an EKG and troponin which were unremarkable. He was admitted to the cardiac unit at UIHC through t he ER as a precaution, for standard rule-out myocardial in farction procedures. He was discharg ed per the cardiology team on 08/ 14/10 without further complications and did not have a myocardial infarction. A nuclear medicine stress test was negative at the end of his hospital stay. The event was deemed unlikely to be related to the Ad5-PSA vaccine.

This is the first incidence of che st pains during this Phase II trial. The patient was enrolled in Arm B of Protocol #1 of the Phase II trial and had received androgen deprivation therapy (ADT) 14 days prior to the initial vaccination with the Ad5-PSA vaccine. The ADT included the LHRH agonist Zoladex plus the anti-androgen Casodex. The package insert for Casodex indicates that 8% of patients on ADT of LHRH agoni sts and C asodex experienced chest pains (http://www1.astrazeneca-us.com/pi/casodex.pdf).

Patient in Protocol #2

77 year old male subject enrolled in this study received the third of three study injections on 8/12/10. He had a history of coronary artery disease with stenting, the last stent placed approximately two years ago. In addition, his medical history includes prostate cancer; hearing loss; placement of intra-ocular lens post cataract, vitreous detachment, and presbyopia; hyperlipidemia, old myocardial infarction and related sequelae, atherosclerosis, hypertension, angina pectoris and atypical chest pain; gastroesophageal reflux disorder, hemorrhoids, diverticulosis; dysthymia, major depressive disorder in remission; lumbago and joint pain; cellulitis (resolved); alcohol dependency in remission; tobacco use disorder. Medications included Goserelin, Ergocalciferol, Cholecalciferol, Aspirin, Calcium with Vitamin D, Cholestyramine, Clopidogrel, Gabapentin, Gemfibrozil, Isosorbide Mononitrate, Lisinopril, Metoprolol, Nitroglycerin tabs, Nortryptyline, Omeprazole, Terazosin, Triamcinolone, Pravastatin.

This subject had received his third study injection on 8/12/10 and had been discharged 8/13/10. On 8/16/10 he arrived at his primary care clinic and reported that he had experienced chest pain with jaw numbness while driving to the clinic, took nitroglycerin and aspirin, and the pain went away quickly; he was not short of breath nor diaphoretic, but was started on oxygen, per the primary care clinician's note in CPRS. That note further states that the subject reported that his chest pain had been increasing in frequency over the last three months and that even though he had received a recommendation to call cardiology by the hematology/oncology clinic, he chose not to. (There is a study team note in CPRS dated July 29, 2010, signed by the research nurse and also by the primary care provider in which it is documented that the subject reported on Day 44 of the study that he had been having more chest pain episodes "in the last four months or so" and that he knew he needed to call the cardiologists.) The primary care clinician consulted cardiology and sent the subject to the ER for accelerated angina.

Per CPRS documentation the subject reported to the ER provider that he had been having substernal chest pain and pressure exclusively at rest for about three months and that this episode was the same as past episodes; subject at that point was chest pain free, without palpitations, lightheadedness, or dyspnea. This clinician assessed the subject condition as "concerning for unstable angina" and admitted the subject to the VAMC for observation and standard rule-out myocardial infarction and ischemia procedures. Cardiology note in CPRS reports EKG was negative, troponin was negative twice, stress test was negative, no reversible defect was noted. Cardiology planned to continue the aspirin, clopidogrel, metoprolol, lisinopril, and isosorbide, and to consider increasing the latter if chest pain frequency increases but that this was not indicated at this time since the episodes occur once every 2-3 weeks; cardiology also increased the subject's pravastatin since the low density lipoprotein was greater than 90 and not at goal. The subject was discharged to home on 8/17/10 and directed to follow up with cardiology as outpatient. This is the second incidence of chest pains during this Phase II trial. The patient has hormone-refractory prostate cancer with prior androgen-deprivation therapy (ADT). He no longer is on Casodex

**KEY RESEARCH ACCOMPLISHMENTS:**

For each patient we collected serum for future measurements of anti-PSA and anti-adenovirus antibodies, isolated lymphocytes from the peripheral blood for the measurement of anti-PSA and anti-adenovirus T cell responses, and measured serum levels of PSA and PAP.

**PSA Doubling Times (PSADT) –** One of the measurements used to follow the clinical pattern of prostate cancer before and after therapy is the change in doubling time of the serum PSA levels. We have evaluated the PSADT of some of the patients in the tria, but have not done so for patients in this grant year due to a change in laboratory personnel. The data for the patients enrolled in the current year are being collected and PSADT will be calculated and reported in future quarterly and annual reports. Table 2 demonstrates that of the nine evaluable patients, on whom we had sufficient data to calculate both pre-vaccination and post-vaccination PSADT values, seven or 78%, either had an increase in PSADT or a decline in total PSA and two or 22% had a decrease in the PSADT values. There are four enrolled patients that have too few post-vaccination PSA values to calculate their after treatment PSADT.

**Table 2**
**PSA Doubling Times (PSADT)**

| Patient | PSADT | | Percent Change |
|---|---|---|---|
| | Pre-Vaccination | Post-Vaccination | |
| | | | |
| ***APIIAHN-09*** | ***16.5*** | ***(PSA decline)*** | ***(-8.9%)***[a] |
| APIIAHN-10 | 13.44 | ***(PSA decline)*** | ***(-9.3%)*** |
| APIIAHN-11 | 9.96 | Too few to calc. | --- |
| APIIAHN-12 | 52.2 | Too few to calc. | --- |
| APIIAHN-13 | 18.59 | Too few to calc. | --- |
| APIIB-12 | 12.7 | 72.3 | +469.8% |
| APIIB-13 | 1.6 | 5.6 | +250.0% |
| APIIB-14 | 30.2 | 20.5 | -32.1 |
| APIIB-15 | 6.3 | ***(PSA decline)*** | ***(-13.0%)*** |
| APIIB-16 | 12.2 | ***(PSA decline)*** | ***(-1.7%)*** |
| APIIB-17 | 8.63 | 5.8 | -33.4 |
| APIIB-18 | 7.11 | 14.01 | +97.47 |
| APIIB-19 | 17.7 | Too few to calc. | --- |
| | | | |
| Overall as of 4/15/11 – 7/9 evaluable patients (78%) demonstrated either an increase in PSADT or a decline l total PSA and 2/9 patients (22%) demonstrated a decrease in PSADT. | | | |

**ELISPOT Analysis of Anti-PSA T Lymphocytes Immune Responses –** Since the primary arm of the immune response to tumor associated antigens has been documented as the T cell-mediated response, we examined the development of the responses over time after the initiation of vaccination. At each patient visit we obtained peripheral blood and isolated the lymphocytes by density gradient centrifugation. The majority of the lymphocytes were suspended in a cryopreservative solution and stored in liquid nitrogen for future analyses. At the end of the first 12 months following the initiation of therapy all of the samples for each patient will be thawed and an ELISPOT assay performed at one time. This is done to avoid inter-assay variability and will allow us to accurately compare the responses at each time point. When the lymphocyte yields were large such that we were able to cryopreserve sufficient numbers of cells for that single assay and have extra cells, we performed the ELISPOT assays on the freshly isolated cells. This is permitting us to obtain some preliminary measure of the anti-PSA T cells responses for the patients at the appropriate time points. However, the more definitive assays will be those performed on the stored cells after the 12 month time point. In the first year we did not do the 12 month assays, but report here the results of assays

performed on patient samples when sufficient cells were available. Again, because of a change in laboratory personnel, ELISPOT data are not available for the patients enrolled in the current year. They are being analyzed and will be presented in future quarterly and annual reports. Table 3 provides the data for the patients previously analyzed. For the patients in protocol #1, Arm A, 2/2 (100%) developed positive anti-PSA T cell responses. For patients in protocol #1, Arm B, 2/2 (100%) developed positive anti-PSA T cell responses. For patients in protocol #2, 3/6 (50%) developed strong responses and 2/6 (33%) developed modest responses. For all patients in this protocol 5/6 (83%) developed positive anti-PSA T cells responses. For all patients in both protocols, 90% developed some level of anti-PSA T cell responses, with 70% developing strong responses.

**Table 3**
**Ad/PSA Phase II Clinical Trial**
**ELISPOT Analysis of T Cell Responses**

| Patient | T Cell Frequency | | Response |
|---|---|---|---|
| | Pre-Vaccination | Post-Vaccination | |
| | | | |
| APIIAHN-01 | 1/2X10E6 | 1/24,096 | + |
| APIIAHN-02 | 1/33,000 | 1/12,000 | + |
| APAADT-01 | 1/500,000 | 1/10,050 | + |
| APAADT-02 | 1/46,512 | 1/7,463 | + |
| APIIB-01 | 1/11,426 | 1/4,357 | - |
| APIIB-02 | 1/1x10E8 | 1/10,870 | + |
| APIIB-04 | 1/500,000 | 1/8,511 | + |
| APIIB-05 | 1/130,000 | 1/2,850 | + |
| APIIB-06 | 1/154,000 | 1/51,300 | +/- |
| APIIB-07 | 1/133,000 | 1/64,500 | +/- |

**REPORTABLE OUTCOMES:**

Presentation of results from the Phase II trial of the Ad/PSA vaccine at the annual meeting of the American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO), the ASCO Genitourinary Malignancies Conference, and the Fall Symposium of the Society for Basic Urologic Research (SBUR), the North Central Section of the American Urologic Association (AUA), and the DOD's IMPaCT meeting.

**CONCLUSION:**

Patients were enrolled in both protocols, vaccinated three times and followed by return visits to the University of Iowa Hospitals and Clinics and Iowa City VA Medical Center. No serious vaccine-related adverse events were reported for any of the patients. In the analysis of serum PSA and immune responses to PSA following the vaccinations, 67% of the patients demonstrated an increase in PSADT and 90% developed some level of anti-PSA T cell responses, with 70% developing strong responses.

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